ORIGINAL ARTICLE

Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus

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Aims: To evaluate the risk of the stomach and oesophageal adenocarcinomas associated with farming and agricultural pesticide use.

Methods: Population based case-control study in eastern Nebraska. Telephone interviews were conducted with men and women diagnosed with adenocarcinoma of the stomach (n = 170) or oesophagus (n = 137) between 1988 and 1993, and controls (n = 502) randomly selected from the same geographical area. Unconditional logistic regression was used to calculate adjusted odds ratios (ORs) for farming and for use of individual and chemical classes of insecticides and herbicides, including pesticides classified as nitrosatable (able to form N-nitroso compounds on reaction with nitrite). Non-farmers were used as the reference category for all analyses.

Results: Ever living or working on a farm, duration of farming, and size of the farm were not associated with stomach or oesophageal adenocarcinomas. There was no association for either cancer with ever-use of insecticides (stomach OR 0.9, 95% CI 0.6 to 1.4; oesophagus OR 0.7, 95% CI 0.4 to 1.1) or herbicides (stomach OR 0.9, 95% CI 0.5 to 1.4; oesophagus OR 0.7, 95% CI 0.4 to 1.2). Likewise, individual pesticides, including individual nitrosatable pesticides, were not significantly associated with risk.

Conclusions: No significant associations were found between specific agricultural pesticide exposures and the risk of stomach or oesophageal adenocarcinomas among Nebraska farmers.

In a meta-analysis of 29 studies, farmers had a small but marginally significant increased risk of stomach cancer, although there was considerable heterogeneity across studies.[1] Excess risks have been seen with different study designs, in different time periods, and in various countries, although negative reports have been published and there is some evidence of confounding due to dietary factors and rural residence.[2] Exposures to pesticides, organic and inorganic dusts, fertilisers, and diesel fuel have been suggested as contributing to an increased risk of stomach cancer among farmers, although few studies have evaluated specific exposures among farmers.[3]

With few exceptions,[4 5] oesophageal cancer risk is lower among farmers compared with the general population or other occupational groups.[1] However, most studies have not evaluated oesophageal cancer by histological type, and the incidence of adenocarcinomas of the oesophagus and stomach cardia has risen since the mid-1970s in the United States[6] and other western countries. Obesity, smoking, and gastro-oesophageal reflux account for a large proportion of these cancers,[7–9] but do not explain all of the increase. A recent case-control study in the United States[10] evaluated job histories separately for oesophageal squamous cell and adenocarcinomas and found no association for either cancer with employment as a farm worker or for work in agriculture. Specific farming exposures have not been evaluated for oesophageal adenocarcinomas.

Epidemiological studies[11] provide some support for an association between exposure to pesticides—mostly insecticides of organochlorine origin and phenoxy acid herbicides—and risk of stomach cancer. Increased stomach cancer risk has been observed among many but not all cohorts of herbicide applicators and manufacturers[12] and insecticide manufacturers.[13] In a mortality study of aerial pesticide applicators and flight instructors, risks of both stomach and oesophagus cancer was increased.[14] However, few studies have evaluated cancer risk and specific pesticide exposures.

In the 1970s, it was shown that some pesticide formulations were contaminated with nitrosamines.[15] The contamination occurred in the manufacturing process or through the reaction of amine containing pesticides with nitrite that was used as a preservative and corrosion inhibitor.[16] Many pesticides contain amine or amide groups which can react with nitrite and therefore are potential amine precursors for the formation of N-nitroso compounds (NOC) in vivo.[17] More than 300 pesticide formulations have been surveyed for the presence of nitrosamines or their ability to react with nitrite.[18–20] Nitrosamine contamination was found in many pesticides commonly used in agriculture; therefore, farmers and other pesticide applicators were likely to have been exposed. Regulations were implemented by the US Environmental Protection Agency in the early 1980s to reduce the likelihood of nitrosamine contamination.[21]

Many NOC are potent animal carcinogens for the stomach, oesophagus, and other organ sites.[22–24] Specific NOC have been classified by International Agency for Research on Cancer as probably carcinogenic to humans on the basis of sufficient evidence of carcinogenicity in experimental animals and limited evidence of carcinogenicity in humans.[25] To our knowledge, exposure to nitrosatable pesticides (that is, pesticides able to form N-nitroso compounds on reaction with nitrite) has not been evaluated as a risk factor for stomach or oesophageal cancers in an epidemiological study.

We conducted a population based case control study in Nebraska to determine whether agricultural exposures were associated with the risk of adenocarcinomas of the stomach and oesophagus. An additional aim of our study was to evaluate exposure to NOC and NOC precursors and risk of these cancers. Here we present results for agricultural pesticide use, including use of nitrosatable pesticides.

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Main messages

- No papers have been published about the hypothesised relation between exposure to nitrosatable pesticides and risk of stomach and oesophageal cancers.
- Results suggest that exposure to agricultural pesticides including nitrosatable pesticides, does not play a role in the development of adenocarcinomas of the stomach and oesophagus.

Policy implications

- Further studies are warranted to evaluate risk overall and among potentially high risk subgroups.

METHODS
Study population
The study population and methods for this population based case-control study have been described in detail.[26] Briefly, incident cases of stomach and oesophageal cancer cases were identified from the Nebraska Cancer Registry (1988–90) or by review of discharge diagnosis and pathology records at 14 hospitals (1991–93), that accounted for about 90% of the stomach and oesophageal cancer diagnoses in the eastern 66 counties in Nebraska. Only newly diagnosed cases with confirmed adenocarcinoma of the stomach or oesophagus were retained in the analysis. Eligible cases were white male or female residents of these counties, aged 21 years or older. Cases were limited to whites because the controls were sampled from a previous study that only included whites due to the expected small numbers of other ethnic groups. A series of adult glioma cancer cases was also included in the study.

To reduce the cost of the study, controls were randomly selected from a group of controls interviewed in 1986–87 for a population based case-control study of haematopoietic cancers in Nebraska[27] in the same 66 counties. Controls under the age of 65 years were selected from the general population by random digit dialling.[28] Subjects aged 65 years and over were identified from Health Care Financing Administration Medicare files. Controls for deceased cases were selected from Nebraska mortality records with the additional matching factor of year of death. Controls selected for this study were frequency matched by gender and age (five year age groups) to the combined distribution of the stomach, oesophagus, and glioma cases.

Interviews
Cases and controls or their next-of-kin were interviewed by telephone during 1992–94. Interviews included information about basic demographic characteristics, smoking and alcohol consumption, a family history of cancer, a complete residential and occupational history, and other factors. Dietary information was obtained using a modified version of the Health Habits and History Questionnaire.[29] Among those who reported living or working on a farm, we asked a detailed history of pesticide use on the farm as well as years of farming activity and the size of the farm where they lived or worked the longest. The pesticide list for the questionnaire was developed with the assistance of local agricultural experts, and included 16 major insecticides and 14 herbicides used on Nebraska crops over the previous 40 years. All of the questions about pesticide use were for the time period before 1985, the time frame of the previous study.

A total of 170 stomach cancer cases, 137 oesophageal cancer cases, and 502 controls completed interviews with overall response rates of 79%, 88%, and 83% respectively. The response rate of controls in the previous study was 87%; therefore, the adjusted rate was 72% for re-interviewed controls in the current study. Because of the poor prognoses of these cancers, interviews were conducted with a proxy or the next-of-kin for 76% of oesophageal adenocarcinoma cases and 80% of stomach cancer cases. A total of 61% of control interviews involved proxy respondents. Living controls were over sampled to allow for more study power in subgroup analyses by respondent type. Among controls, spouses (46%), children (36%), and parents (10%) were the major proxy respondents. Among stomach and oesophageal cases respectively, spouses (35%, 62%), children (46%, 28%), and parents (7%, 11%) were proxy respondents. Other relatives or friends served as proxies for remaining cases and controls.

Data analysis
Individual pesticides were grouped into insecticides (aldrin, carbaryl, carbofuran, chlordane, copper acetoarsenite, DDT, diazinon, dieldrin, famphur, fonofos, heptachlor, lindane, malathion, nicotine, phorate, terbufos) and herbicides (2,4,5-T, 2,4-D, alachlor, atrazine, chloramben, cyanazine, dicamba, EPTC, glyphosate, metolachlor, metribuzin, pendimethalin, propachlor, trifluralin). We also classified the pesticides into their chemical families: carbamate insecticides (carbaryl, carbofuran), organochlorine insecticides (aldrin, chlordane, DDT, dieldrin, heptachlor, lindane), organophosphorus insecticides (diazinon, famphur, fonofos, malathion, phorate, terbufos), acetanilide herbicides (alachor, metolachlor, propachlor), benzoic acid herbicides (chloramben, dicamba), dinitroaniline herbicides (pendimethalin, trifluralin), phenoxy herbicides (2,4,5-T, 2,4-D), triazine herbicides (atrazine, cyanazine, metribuzin). We estimated the ORs for stomach and oesophageal adenocarcinomas for individual insecticides and herbicides and for the chemical family groupings. Subjects who did not live on a farm after age 18 (n = 139) were evaluated separately because their reported pesticide use was of short duration and their exposure information was likely to have been poorer than those who farmed as adults.

Additionally, through a review of the literature and the expert judgment of an NOC chemist (W Lijinsky) we grouped the pesticides according to their ability to react with nitrite to form the N-nitroso derivative and the likely carcinogenicity of the nitrosatable derivative as determined from animal studies. For nitrosatable pesticides that had not been tested in animals, a judgement was made (by WL) as to their likely carcinogenicity based on the stability of the N-nitroso derivative and the structural similarity to tested compounds. The nitrosatable pesticide group included pesticides that may have been contaminated with NOC during manufacturing or storage before the mid-1980s.[18–20]

Of the 16 insecticides, four were nitrosatable (carbaryl, carbofuran, famphur, nicotine), whereas 10 of the 14 herbicides were nitrosatable (2,4,5-T, 2,4-D as dialkylamine salts, which are the source of nitrosamine contamination, atrazine, cyanazine, dicamba, EPTC, glyphosate, metolachlor, propachlor, trifluralin). Only five of the nitrosatable derivatives of the herbicides (2,4,5-T, 2,4-D, EPTC, glyphosate, trifluralin), but all four nitrosatable derivatives of the insecticides had evidence or were judged to be likely to be animal carcinogens. We calculated ORs for the total number of nitrosatable pesticides and for the total years of nitrosatable pesticides use. We used the median values among nitrosatable pesticide users to classify subjects into a low and high category of nitrosatable use.

We used unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) with Stata software (version 7.0).[30] All significance tests were two sided ($\alpha = 0.05$). The ORs for farming activity and pesticide use were calculated using non-farmers as a reference group.

All ORs were adjusted for the matching factors of age ($\leqslant 54$, 55–69, $\geqslant 70$) and gender. We evaluated as possible confounder variables that were significantly associated with risk of each cancer. These included body mass index (BMI), smoking, alcohol consumption, educational level, family history of stomach or oesophageal cancer, respondent type, dietary intake of vitamin A and C, β-cryptoxanthin, riboflavin, folate, zinc, dietary fibre, protein, and carbohydrate.[31] Variables were retained in models as confounders when inclusion changed the value of the OR by more than 10% in any exposure category. Assigning scores to the categorical variables and treating the scored variables as continuous variables in the logistic analyses obtained tests for trend. We also calculated ORs separately by respondent type. We report the results only when the pattern in the ORs differed by respondent type; this occurred for some analyses of the chemical families including the nitrosatable pesticides.

RESULTS

Table 1 shows the characteristics of the cases and controls. Compared with controls, stomach cancer cases were significantly older, less likely to be alcohol drinkers, and college graduates. Among oesophageal cases there were significantly more men, smokers, and individuals with a higher BMI.

Table 2 shows the adjusted ORs for stomach and oesophageal cancer by farming characteristics. There was no association between ever living or working on a farm and risk of stomach and oesophageal cancers among those who only lived or worked on a farm before age 18 and among adult farmers. We observed no statistically significant ORs by

duration of farming and farm size for either cancer among those who farmed as adults.

Table 3 presents ORs for stomach and oesophageal adenocarcinomas and ever-use of pesticides by chemical family among adult farmers. Pesticide use among those who only lived or worked on a farm during childhood was uncommon, which did not allow evaluation of risk among this group. There was no association with ever-use of insecticides and herbicides and stomach cancer risk, whereas ORs were slightly inverse for oesophageal cancer. Benzoic acid herbicide use showed a significant inverse association with stomach cancer (OR = 0.3; 95% CI 0.1 to 0.8). No other insecticide or herbicide groups were significantly associated with risk of either cancer. The results for oesophageal cancer and some of the chemical families of pesticides were somewhat different among self and proxy respondents. The ORs among self respondents were 1.6 (95% CI 0.6 to 4.4), 1.5 (95% CI 0.5 to 4.7), and 2.0 (95% CI 0.7 to 5.8) for use of the organochlorine insecticides, benzoic acid herbicides, and acetanilide herbicides, respectively. Among proxy respondents the associations were inverse: ORs were 0.6 (95% CI 0.3 to 1.2), 0.8 (95% CI 0.3 to 2.1), and 0.6 (95% CI 0.3 to 1.6) for organochlorine insecticides, benzoic acid herbicides, and acetanilide herbicides, respectively.

The ORs for ever-use of specific pesticides are presented in table 4 if there were five or more exposed cases. None of the individual pesticides, including nitrosatable pesticides, were associated with risk of either cancer. Overall, the total number of nitrosatable pesticides and total years of nitrosatable pesticides use were not associated with risk of stomach or oesophageal cancer risk (table 5). We also evaluated exposure as a continuous variable and found no association. However, the patterns in the ORs for oesophageal cancer were somewhat different among self and proxy respondents. The OR for use of four or more nitrosatable pesticides was 1.8 (95% CI 0.6 to 5.2) among self respondents and 0.5 (95% CI

Table 1 Characteristics of stomach and oesophageal cancer cases, and controls

Characteristics	Controls (n = 502) No.	%	Stomach cancer (n = 170) Cases	%	Oesophagus cancer (n = 137) Cases	%
Age						
$\leqslant 54$	174	34.6	22	12.9	35	25.5
55–69	168	33.5	58	34.1	63	46.0
$\geqslant 70$	160	31.9	90	53.0	39	28.5
Gender						
Male	284	56.6	97	57.1	121	88.3
Female	218	43.4	73	42.9	16	11.7
Smoking						
Never	230	48.0	87	54.7	29	22.7
<30 cigarettes/day	171	35.7	47	29.6	63	49.2
$\geqslant 30$ cigarettes/day	78	16.3	25	15.7	36	28.1
Alcohol						
Never	195	39.5	73	43.2	30	22.2
Current	162	32.8	25	14.8	26	19.3
Past	137	27.7	71	42.0	79	58.5
Respondent type						
Self	198	39.4	34	20.0	33	24.1
Proxy	304	60.6	136	80.0	104	75.9
Education						
<College	294	58.6	119	70.0	85	62.0
$\geqslant$College	208	41.4	51	30.0	52	38.0
Body mass index (kg/m^2)						
$\leqslant 23.0$	159	32.5	49	29.7	24	17.8
23.1–25.0	106	21.7	25	15.2	26	19.3
25.1–27.5	115	23.5	45	27.3	39	28.8
$\geqslant 27.6$	109	22.3	46	27.8	46	34.1
Family history of gastric or oesophageal cancer*						
No	233	50.8	54	35.5	60	46.5
Yes	226	49.2	98	64.5	69	53.5

*Ever first degree relative with stomach or oesophageal cancers.

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) for stomach and oesophageal cancer by farming activity

		Stomach cancer			Oesophageal cancer		
	Controls	Cases	OR*	95% CI	Cases	OR*	95% CI
Non-farmers	184	59	1.0	Ref†	62	1.0	Ref†
Farmers							
Only before age 18‡	97	23	0.7	0.4 to 1.2	19	0.6	0.3 to 1.1
Adult farmers§	221	88	0.9	0.6 to 1.3	56	0.7	0.5 to 1.2
Adult farmers							
Years farmed							
⩽24	73	18	0.7	0.4 to 1.2	19	0.8	0.4 to 1.4
25–54	70	31	1.0	0.6 to 1.7	18	0.8	0.4 to 1.6
⩾55	75	38	1.0	0.6 to 1.6	19	0.7	0.4 to 1.3
Average acres							
<170	79	36	1.0	0.6 to 1.7	18	0.7	0.4 to 1.3
170–320	63	25	0.8	0.5 to 1.4	15	0.7	0.4 to 1.4
>320	54	18	0.8	0.4 to 1.6	12	0.6	0.3 to 1.2

*Odds ratio adjusted for age and gender.
†Reference category: non-farmers.
‡Subjects who lived or worked on a farm only before age 18.
§Subjects who had lived or worked on a farm as an adult (>18 years).

0.2 to 1.2) among proxies. The results for oesophageal cancer by respondent type for the total years of nitrosatable pesticides use and the subgroup of nitrosatable pesticides that showed evidence of carcinogenicity were similar in that ORs were increased among self respondents and inverse among proxy respondents (data not shown).

DISCUSSION

We found no evidence of an increased risk of adenocarcinoma of stomach or oesophageal cancer among farmers with the duration of farming and farm size. Furthermore, use of specific chemical families of pesticides and the group of nitrosatable pesticides also showed no association with risk of either cancer. Except for a significant inverse association between benzoic acid herbicides use and stomach cancer, we found no significant association with use of any individual pesticide. The lack of biological plausibility for an inverse association between stomach cancer and benzoic acid herbicides and the small number of cases suggests a non-causal interpretation.

A review of studies of herbicide applicators and producers[12] found increased risks of stomach cancer in seven cohort studies (one was significantly increased) and no association in three studies. A review of the cohort studies of insecticide manufacturers and applicators found increased stomach

cancer mortality; however, excesses were small and were based on a small number of deaths.[13] Two additional studies found increased risks of stomach cancer. Risk was increased after accounting for a 20 year latency among chlorophenol manufacturers exposed to chlorinated dioxins.[32] A population based case-control study of stomach cancer in Sweden found an increased risk among those exposed to phenoxy acid herbicides.[33] In contrast, we found no association between use of phenoxy acid herbicides and either stomach or oesophageal cancer. Most of these studies either did not report oesophageal cancer risk or found an increased association. The hypothesised explanation of decreased oesophageal cancer risk in these studies was the lower prevalence of smoking among farmers in most countries.[34]

Exposure to nitrosatable pesticides or to pesticides contaminated with nitrosamines has been suggested as a possible explanation for the higher rates of stomach cancer among farmers[2] because of the long standing hypothesis that NOC exposure is a risk factor for this cancer based on animal studies and limited epidemiological evidence.[22 35] Because most N-nitroso compounds are generally systemic carcinogens and not locally acting, it is possible that these contaminants in pesticide formulations contribute to the induction of tumours other than those of the stomach and

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs) for stomach and oesophageal cancer for ever-use of pesticides classes among adult farmers

		Stomach cancer			Oesophageal cancer		
	Controls	Cases	OR*	95% CI	Cases	OR*	95% CI
Non-farmers	184	59	1.0	Ref†	62	1.0	Ref†
Insecticides	129	49	0.9	0.6 to 1.4	29	0.7	0.4 to 1.1
Farmers, no use	65	28	0.8	0.5 to 1.4	17	0.8	0.4 to 1.6
Carbamate	61	16	0.7	0.4 to 1.3	16	0.8	0.4 to 1.5
Organochlorine	83	29	0.8	0.5 to 1.4	20	0.7	0.4 to 1.3
Organophosphorus	70	22	0.9	0.5 to 1.5	16	0.6	0.3 to 1.2
Herbicides	111	40	0.9	0.5 to 1.4	29	0.7	0.4 to 1.2
Farmers, no use	83	32	0.7	0.4 to 1.3	17	0.6	0.3 to 1.2
Acetanilide	51	8	0.5	0.2 to 1.0	16	0.8	0.4 to 1.6
Benzoic acid	43	4	0.3	0.1 to 0.8	14	0.9	0.4 to 1.8
Dinitroaniline	26	7	0.8	0.3 to 2.1	6	0.7	0.3 to 1.8
Phenoxy	90	29	0.8	0.5 to 1.5	20	0.7	0.4 to 1.2
Triazine	61	19	0.8	0.5 to 1.5	15	0.6	0.3 to 1.2

*Odds ratio adjusted for age and gender.
†Reference category: non-farmers.

Table 4 Odds ratios (ORs) and 95% confidence intervals (CIs) for stomach and oesophageal cancer by ever-use of individual pesticides among adult farmers

		Stomach cancer			Oesophageal cancer		
	Controls	Cases	OR*	95% CI	Cases	OR*	95% CI
Non-farmers	184	59	1.0	Ref†	62	1.0	Ref†
Herbicides							
2,4,5-T‡§	28	8	0.7	0.3 to 1.7	7	0.7	0.3 to 1.9
2,4-D‡§	89	27	0.8	0.4 to 1.3	20	0.7	0.4 to 1.2
Alachlor	40	7	0.5	0.2 to 1.3	12	0.8	0.4 to 1.7
Atrazine‡	55	18	0.9	0.5 to 1.6	15	0.7	0.4 to 1.4
Cyananzine‡	20	1	0.2	0.1 to 1.3	5	0.8	0.3 to 2.4
Dicamba‡	35	4	0.3	0.1 to 1.0	13	0.9	0.5 to 1.9
EPTC‡§	28	6	0.6	0.2 to 1.5	9	0.8	0.3 to 1.8
Glyphosate‡§	46	12	0.8	0.4 to 1.5	12	0.7	0.3 to 1.4
Propachlor‡	27	5	0.5	0.2 to 1.4	10	0.9	0.4 to 2.1
Trifluralin‡§	24	6	0.8	0.3 to 2.1	5	0.7	0.2 to 1.9
Insecticides							
Aldrin	30	6	0.4	0.2 to 1.1	8	0.8	0.3 to 1.8
Carbaryl‡§	47	9	0.5	0.2 to 1.2	12	0.7	0.4 to 1.5
Carbofuran‡§	36	9	0.7	0.3 to 1.6	11	0.8	0.4 to 1.8
Chlordane	40	15	0.9	0.5 to 1.8	10	0.6	0.3 to 1.4
DDT	65	27	0.9	0.5 to 1.6	16	0.8	0.4 to 1.5
Diazinon	35	6	0.5	0.2 to 1.2	10	0.8	0.4 to 1.8
Dieldrin	23	6	0.6	0.2 to 1.5	5	0.5	0.2 to 1.5
Fonofos	26	5	0.5	0.2 to 1.4	7	0.8	0.3 to 1.9
Lindane	36	8	0.5	0.2 to 1.2	8	0.6	0.3 to 1.5
Malathion	46	14	0.8	0.4 to 1.6	12	0.7	0.4 to 1.5
Nicotine‡§	23	10	0.9	0.4 to 2.0	4	0.5	0.2 to 1.5
Phorate	26	6	0.6	0.2 to 1.7	10	1.1	0.5 to 2.6
Terbufos	29	5	0.6	0.2 to 1.6	6	0.6	0.2 to 1.5

Pesticides with more than five cases either stomach or oesophagus are shown.
*Odds ratio adjusted for age and gender.
†Reference category: non-farmers.
‡Nitrosatable pesticides.
§Nitrosatable pesticides with experimental evidence of carcinogenicity or were likely to be carcinogenic.

oesophagus. A positive association between occupational nitrosamine exposure and having detectable O^6-methylguanine adducts in peripheral blood has been found in rubber industry workers.[36] Because these DNA adducts have mutagenic potential and may play a role in carcinogenesis,[37] this finding supports the biological plausibility of an

Table 5 Odds ratios (ORs) and 95% confidence intervals (CIs) for stomach and oesophageal cancer by number of nitrosatable pesticides used and years of nitrosatable pesticides used among adult farmers

	Cases	Controls	OR*	95% CI	p value for trend
Total number of nitrosatable pesticides usde‡					
Stomach					
Non-farmers	59	184	1.0	Ref†	
0	52	122	0.9	0.5 to 1.4	
1–3	21	38	1.2	0.6 to 2.2	
≥4	15	61	0.7	0.3 to 1.3	0.436
Oesophagus					
Non-farmers	62	184	1.0	Ref†	
0	33	122	0.8	0.5 to 1.4	
1–3	6	38	0.5	0.2 to 1.2	
≥4	17	61	0.7	0.4 to 1.4	0.206
Total year of nitrosatable pesticides used§					
Stomach					
Non-farmers	59	184	1.0	Ref†	
0	70	159	0.9	0.6 to 1.4	
≤20	9	35	0.7	0.3 to 1.7	
>20	9	27	0.8	0.3 to 1.8	0.414
Oesophagus					
Non-farmers	62	184	1.0	Ref†	
0	42	159	0.8	0.5 to 1.3	
≤20	5	35	0.4	0.2 to 1.1	
>20	9	27	0.8	0.4 to 1.9	0.203

*Odds ratio adjusted for age and gender.
†Reference category: non-farmers.
‡Sum of total number of nitrosatable pesticides used.
§From first to last year of nitrosatable pesticides used.

association between NOC exposure and human cancer development.

Humans are exposed to preformed N-nitroso compounds from a variety of sources.[38] [39] Dietary intakes are estimated to contribute the majority of NOC exposure.[39] However, nitrate exposure in drinking water can be a significant contributor to total nitrate intake and to potential NOC exposure when levels are at or above the maximum contaminant level of 10 mg/l.[40] [41] In this study population, dietary sources of NOC were not significantly associated with risk of stomach and oesophagus cancer,[31] nor were nitrate levels in public water supplies (M Ward, unpublished data). It is also important to consider that the routes of exposure are different for nitrosatable pesticides (inhalation and dermal) versus dietary NOC or NOC precursors (ingestion). Relative to other sources of NOC exposure, occupational exposure via agricultural pesticide use may be small and for this reason it may not be significant for the development of stomach or oesophageal cancer. However, that does not rule out the possibility of an increased risk among those with higher exposures or among subgroups with increased ability to metabolise nitrosamines.[42–44]

The limitations of this analysis were the possible misclassification of pesticide exposure and the generally small number of farmers exposed to some of the individual pesticides. Although the assessment of nitrosability of each pesticide was based on chemical structure and a detailed literature review, misclassification of exposure may have occurred because the nitrosamine contamination of the pesticide formulation was likely to be variable, and we also lacked information on the ease of nitrosation for some pesticides. This potential misclassification would be expected to be non-differential for cases and controls and the observed effect estimates would likely be biased towards the null. Misclassification of exposure is also possible because data related to past exposure to pesticides were obtained by interviews with study subjects or their proxy respondents. In our study, proxies were more likely to provide ''don't know'' responses and were less likely to report use of specific pesticides than subjects themselves, as has been reported by others.[45] [46] However, in spite of some evidence of underreporting of exposure by proxies, the different pattern by respondent type was limited to oesophageal cancer.

In summary, we found no significant associations between agricultural pesticide exposures and the risk of adenocarcinoma of stomach or oesophagus among Nebraska farmers. However, further evaluation of this hypothesis in larger studies with genetic information on nitrosamine metabolising enzymes is warranted to evaluate risk among potentially high risk subgroups of pesticide applicators.

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Note: Dr William Lijinsky is deceased

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